

## BLADDER CANCER AND CIGARETTE SMOKING IN MALES: A CASE-CONTROL STUDY

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Cigarette consumption was compared between 355 males with cancer of the lower urinary tract and 276 male hospital controls. Both duration of smoking and average daily consumption of cigarettes showed a dose-response relationship with risks of developing bladder cancer. Quitting smoking seems to have a protective role, whereas higher relative risks are associated with an early age at start of smoking. The use of a filter seems to have a weak protective effect.

Epidemiological studies both of the case-control and cohort types have consistently shown that cigarette smoking is a determinant of urinary tract cancer. A unique previous observation suggesting that this might not be the case in the U.K. (1) was contradicted in a more recent study (2). Relative risks for smokers (any amount of tobacco) vs. non-smokers have consistently been in the order of 1.5-3. A dose-response relationship was found when risks were assessed separately for different categories of smokers, with relative risks ranging up to five for life-long smokers of 20 or more cigarettes per day (6). The mechanism of the association is not known: on chemical grounds, the finding of 2-naphthylamine (up to 2 ng/cigarette) and other aromatic amines in tobacco smoke (9) is of interest, but it is difficult to establish whether they explain all of the effect on the urinary tract.

The association between tobacco smoke and cancer of the urinary tract has been confirmed in the first phase of an on-going case-control study in the Province of Torino (10). The present report describes further analyses of this study, considering some biological variables such as age at diagnosis, age at which smoking started, the impact of quitting smoke, as well as the type of cigarettes (filtered/unfiltered) smoked.

### Material and methods

The study is hospital-based and includes residents in the Province of Torino. It started in 1978 and was redesigned early in 1981. In the first phase (10), 225 cases and as many controls were entered: controls were patients attending the two urological departments where cases were recruited; patients with hematuria of unspecified origin, cystitis, cancer at any site, or polyps of the urinary tract were not eligible as controls. Only men aged under 70 were included in this phase: since 1981, the study was extended to women (who are not included in the present report) and to age 75. In addition, interviews of urological controls have been discontinued, whereas a new series was started of randomly chosen controls from five departments of general surgery (excluding cardio- and thoraco-surgery) in the same hospital. In the present analysis, no pathological condition was excluded among these controls: there were 5/51 patients with cancer (3 colon and 2 gastric cancers), and the others were affected by 33 different benign conditions.

The study is on-going. The present report is based on 355 male cases (average age at first diagnosis 57.3 years), 225 male urological con-

**Acknowledgments:** This work was partially supported by Progetto Finalizzato C.N.R. « Controllo della crescita neoplastica » (contracts no. 80.02512.96 and 81.01473.96) and by Associazione Italiana per le Ricerche sul Cancro.

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Received July 6, 1982.

**Table 1 - Total number of cigarettes smoked during life in cases and controls: Age-standardized relative risks (RR).**

Total number of cigarettes (thousands)	Cases	Controls	RR	95 % Confidence limits
Non-smokers	14	48	1.0	—
1 - 72	24	34	2.6	1.1 - 6.1
73 - 144	42	53	2.4	1.1 - 5.1
145 - 216	67	38	5.7	2.8 - 11.6
217 +	208	103	7.0	3.9 - 12.6
Total	355	276		

χ<sup>2</sup> Mantel extension = 7.37.

**Table 2 - Duration of cigarette smoking of cases (Ca) and controls (Con): Age-specific and age-standardized relative risks (RR).**

Smoking duration (years)	Age < 50		Age 50-59		Age 60+		All ages		95 % Confidence limits
	Ca/Con	RR	Ca/Con	RR	Ca/Con	RR	Ca/Con	RR	
Non-smokers	2/7	1.0	3/17	1.0	9/24	1.0	14/48	1.0	—
< 20	6/18	1.2	5/7	4.0	7/9*	2.0	18/34	2.2	0.9 - 5.5
20 - 39			64/57	6.3	24/25	2.6	146/106	4.3	2.3 - 8.3
40 +	64/24	9.3	50/18	15.7	121/70	4.6	177/88	8.0	4.3 - 15.0
Total	72/49		122/99		161/128		355/276		

**Table 3 - Average daily cigarette consumption of cases (Ca) and controls (Con) throughout life: Age-specific and age-standardized relative risks (RR).**

Average cigarettes/day	Age < 50		Age 50-59		Age 60+		All ages		95 % Confidence limits
	Ca/Con	RR	Ca/Con	RR	Ca/Con	RR	Ca/Con	RR	
Non-smokers	2/7	1.0	3/17	1.0	9/24	1.0	14/48	1.0	—
≤ 9	13/12	3.8	13/24	3.0	29/34	2.3	55/70	2.7	1.4 - 5.5
10 - 19	42/17	8.6	70/42	9.4	75/54	3.7	187/113	5.7	3.1 - 10.4
20 +	15/13	4.0	36/16	12.7	48/16	8.0	99/45	9.0	4.6 - 17.8
	(χ <sup>2</sup> Mantel ext. = 1.5)								
Total	72/49		122/99		161/128		355/276		

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trols, and 51 male of controls at interv 185 were interview diagnosis (incident valent; the diagnos histologically confir scopic diagnosis.

All patients were soanel using a stan cluded detailed qu consumption. The consumption up to interview for contr mum-likelihood esti were computed with calculations were Boice's programs (8)

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**Table 4 - Time since q tegory: non-smokers).**

Years since quitting smoking
≤ 2 (including current
3 - 9
10 - 14
15 +
Non-smokers
Total

**Table 5 - Time since q**

Years since quitting smoking
≤ 2 (including current
3 - 9
10 - 14
15 +

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trols, and 51 male surgical controls (average age of controls at interview 57.7 years). Among cases, 185 were interviewed within 6 months of the diagnosis (incident cases) while 170 were prevalent; the diagnosis of 274/355 cases has been histologically confirmed, the others had a cystoscopic diagnosis.

All patients were interviewed by trained personnel using a standard questionnaire which included detailed questions on life-long tobacco consumption. The analyses considered cigarette consumption up to diagnosis for cases and up to interview for controls. Relative risks are maximum-likelihood estimates; 95% confidence limits were computed with Miettinen's formula (7). All calculations were done using Rothman and Boice's programs (8) with a HP-67 calculator.

Originally, some analyses were performed considering separately either incident and prevalent cases or urological and surgical controls. Since in both cases only minor differences were found, results are presented with reference to all cases and controls.

## Results

Relative risks for total number of cigarettes smoked throughout life are given in Table 1. The dose-response relationship is not linear, and this probably reflects the fact that this variable includes 2 different components, i.e., duration and daily dose. Age-standardized relative risks associated only to smoking duration (table 2) and to average number of cigarettes/day (table 3) showed a more satisfactory internal coherence. With the exception of smokers of 20 or more cigarettes/day aged < 50 years, all age-specific relative risks associated to either duration or daily consumption were lowest for people aged 60+ at diagnosis.

Among ex-smokers, risks decreased as time elapsed since quitting (tables 4 and 5). However, quitting smoking is probably confounded by age, duration, and number of cigarettes smoked throughout life. Therefore, risks were standardized by total number of cigarettes: this was done separately for age-classes < 60 and 60+. In the former age-class, risks (relative to current smokers

Table 4 - Time since quitting smoking in cases and controls: Age-standardized relative risks (RR) (reference category: non-smokers).

Years since quitting smoking	No. of cases	No. of controls	RR	95 % Confidence limits
≤ 2 (including current smokers)	278	158	6.0	3.4 - 10.7
3 - 9	28	26	3.7	1.7 - 8.3
10 - 14	13	12	3.6	1.3 - 9.7
15 +	22	32	2.1	0.9 - 4.9
Non-smokers	14	48	1.0	—
Total	355	276		

Table 5 - Time since quitting smoking: Age-specific relative risks (standardized by total amount of cigarettes).

Years since quitting smoking	Relative risk for age at diagnosis/interview	
	< 60	60 +
≤ 2 (including current smokers)	1.0	1.0 (reference category)
3 - 9	0.49	0.77
10 - 14	0.30	1.07
15 +	0.27	0.86

**Table 6 - Age at start of cigarette smoking in cases and controls: age-standardized relative risks (RR) (reference category: non-smokers).**

Age at start (years)	No. of cases	No. of controls	RR	95 % Confidence limits
≤ 12	42	20	7.9	3.6 - 17.6
13 - 16	133	83	5.5	3.0 - 10.4
17 - 20	132	94	4.9	2.6 - 9.2
21 +	34	31	3.8	1.8 - 8.2
Non-smokers	14	48	1.0	—
Total	355	276		

**Table 7 - Age at start of cigarette smoking: age-specific relative risks (standardized by total amount of cigarettes).**

Age at start (years)	Relative risk for age at diagnosis/interview		
	< 50	50-59	60 +
≤ 12	1.0	1.0	1.0 (reference category)
13 - 16	1.36	0.46	0.72
17 +	2.25	0.56	0.62

**Table 8 - Proportion of cigarettes with a filter smoked throughout life in cases and controls: age-specific relative risks (RR) (standardized by total number of cigarettes throughout life; non-smokers are excluded).**

	% cigarettes with filter	No. of cases	No. of controls	RR	95 % Confidence limits
Age < 50	< 50	41	19	1.0	—
	≥ 50	29	23	0.6	0.3 - 1.5
Age 50 - 59	< 50	74	48	1.0	—
	≥ 50	45	34	0.9	0.5 - 1.6
Age 60 +	< 50	111	68	1.0	—
	≥ 50	41	36	0.6	0.4 - 1.1

*Bladder cancer and cigarette*

+quitters since 1-2 years) 0.30 and 0.27 among ex-smokers for 3-9, 10-14 and 15+ years figures among men aged 60 0.86. Only the 0.27 relative < 60 who had quit smoking an upper 95% confidence (0.08-0.85).

Another apparently important which smoking started: a relationship between age at start is obvious (tables 6 and 7). The finding by age and number of cigarettes smoked throughout life cannot be ruled out (relative to smokers starting earlier) following standardization of cigarettes were then estimated relative risks for smokers and 17+ were respectively 4.9 and 3.8 respectively on 33 cases and 27 responding figures were 0.46 (respectively 40 and 65 cases at age 60+ (respectively 60 confidence intervals of all these

The role of a filter was compared by comparing the proportion of cigarettes smoked at least 50% filtered was done separately for the 50-59 and 60+ (table 8). An analysis of people predominately cigarettes were respectively 0.6 and 0.9 thus suggesting a trend consistently recent marketing of the 3 age-classes, people who preferred filtered cigarettes exhibited relative to people who preferred unfiltered cigarettes.

**Discussion**

The present study confirms the association of smoking and daily number of cigarettes smoked with the risk of bladder cancer. In comparison with other studies, relative risks were similar. For example, the relative risk of 1 cigarette/day was around 2 (3), 3.8 in a study in Toronto present study. Also, a higher proportion of the population can be compared (about 77%).

This might reflect a differential of cigarettes smoked in different periods. It is known that in Southern Europe at least

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+quitters since 1-2 years) were respectively 0.49, 0.30 and 0.27 among ex-smokers who had quit for 3-9, 10-14 and 15+ years. The corresponding figures among men aged 60+ were 0.77, 1.07 and 0.86. Only the 0.27 relative risk among men aged < 60 who had quit smoking for 15+ years had an upper 95% confidence limit lower than 1 (0.08-0.85).

Another apparently important factor is age at which smoking started: a negative linear relationship between age at start and relative risks was obvious (tables 6 and 7). However, again, confounding by age and number of cigarettes throughout life cannot be ruled out. Age-specific risks (relative to smokers starting at 12 years of age or earlier) following standardization by total number of cigarettes were then estimated. At age < 50, relative risks for smokers starting at age 13-16 and 17+ were respectively 1.36 and 2.25 (based respectively on 33 cases and 30 cases); the corresponding figures were 0.46 and 0.56 at age 50-59 (respectively 40 and 65 cases) and 0.72 and 0.62 at age 60+ (respectively 60 and 71 cases). Confidence intervals of all these risks included 1.0.

The role of a filter was investigated by comparing the proportion of cases and controls who smoked at least 50% cigarettes with filter: this was done separately for the 3 age-classes < 50, 50-59 and 60+ (table 8). Among controls, the proportion of people predominantly smoking filtered cigarettes were respectively 55%, 41% and 35%, thus suggesting a trend consistent with the relatively recent marketing of filtered cigarettes. In the 3 age-classes, people predominantly smoking filtered cigarettes exhibited risks lower than 1 relative to people predominantly smoking non-filter cigarettes.

### Discussion

The present study confirms that both duration of smoking and daily number of cigarettes are associated with the risk of developing bladder cancer. In comparison with previous investigations, relative risks were somewhat higher. For example, the relative risk for smokers of 10-19 cigarettes/day was around 2 in a study in Boston (3), 3.8 in a study in Toronto (6), and 5.7 in the present study. Also, a higher attributable risk in the population can be computed from our study (about 77%).

This might reflect a different carcinogenic potential of cigarettes smoked in different countries in different periods. It is known that people living in Southern Europe at least in the past smoked

black tobacco more frequently than blond tobacco, in contrast with people living in Northern Europe and the U.S.A. (9).

The slow but obvious decline of relative risks after quitting smoking is similar to the pattern described by Wynder and Goldsmith (11) for bladder cancer and by Doll (5) for lung cancer. The present findings suggest that the impact persists following standardization for total number of cigarettes and that it is concentrated among cancers diagnosed before age 60. Age at which smoking started also seems to be associated to the relative risk for bladder cancer, but this requires confirmation.

It has been postulated (4) that relative risks that increase with increasing age at which smoking started are suggestive of a role of tobacco smoke in « late » stages of carcinogenesis, whereas risks decreasing with age at start would indicate a role of tobacco smoke in « early » stages. Similarly, the hypothesis of an « early » effect is coherent with stability of risks after quitting, whereas the hypothesis of a « late » effect is coherent with a decrease of relative risks after quitting (4). The present data are somewhat contradictory. Among people developing the disease after age 60, results are consistent with the hypothesis of an early effect of tobacco smoke in bladder carcinogenesis. However, among people diagnosed in younger ages, the impact of quitting smoke and of age at start would rather suggest a « late » effect of tobacco in bladder carcinogenesis. Possible explanations for this discrepancy (which requires confirmation) include: a) a different chemical composition of the smoke of cigarettes produced in different calendar periods, b) an age-associated differential in the interaction with other bladder carcinogens and particularly the occupational ones (10).

A protective role of a filter is suggested by the present findings but it seems to be weak, in confirmation of previous findings (6).

### Canero vescicale e fumo di sigarette nei maschi: uno studio caso-controllo

In uno studio caso-controllo in corso tra i residenti nella provincia di Torino, vengono messi a confronto i consumi di sigarette di 355 pazienti maschi affetti da tumori maligni delle basse vie urinarie e di 276 controlli ospedalieri maschi. Sia la durata sia la quantità media giornaliera di sigarette mostrano una relazione dose-risposta con il rischio di contrarre cancro vescicale. La cessazione del consumo sembra svolgere un ruolo protettivo, mentre rischi relativi maggiori sono associati a un'età precoce di inizio del consumo. All'uso di filtro sembra connesso un debole effetto di protezione.

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CARCINOEN  
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There are reports that carcinoen contain carcinoen although not much in these neoplasms or related to the antigen first discovered in gastrointestinal tumors concerning CEA levels usually do not take into determination of possibility of a carcinoen reacting antigen (

The purpose of the study was to determine the tissue localization of carcinoen in serum free from carcinoen antibodies with the aim of a logic evaluation of operative determination of carcinoen in patients. We compared the relationship among carcinoen tissue distribution and carcinoen this antigen into t

## Acknowledgments:

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Received July 14, 1

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